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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,187	07/30/2001	Rosanne M. Crooke	ISPH-0590	2706

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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/918,187	CROOKE ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- *Failure to reply within the set or extended period for reply will, by statute, cause the application to become* ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's amendments filed 10-24-2002 have obviated the restriction requirement set forth in the prior Office actions, mailed 09-24-2002.

Specification

Applicant should note, the sequence listing has been corrected to delete non-ASCII "garbage" at the end of the file. No action is required on the part of Applicant with regard to the sequence listing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the expression of human stearoyl-CoA desaturase in cells or tissues in vitro (cell culture) using antisense, does not reasonably provide enablement for methods of inhibiting the expression of stearoyl-CoA desaturase in vivo (whole organism) and methods of treating a human using antisense. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 15-20 are drawn broadly to inhibition of the expression of human stearoyl-CoA desaturase in any cell *in vivo* (whole organism) for the treatment of any disease or condition that is associated with human stearoyl-CoA desaturase. Claims 17-20 are further drawn to treating any condition associated with sphingosine-1-phosphate lyase that involves abnormal lipid or cholesterol metabolism, atherosclerosis and cardiovascular disease using antisense targeted to a nucleic acid encoding human stearoyl-CoA desaturase.

The specification provides examples wherein chimeric phosphorothioate antisense targeted to a nucleic acid encoding human stearoyl-CoA desaturase inhibited the expression human stearoyl-CoA desaturase *in vitro* (cell culture) in human cell lines. The specification does not demonstrate any correlation with the inhibition of human stearoyl-CoA desaturase in cell culture and a treatment effect for any disease or condition associated with human stearoyl-CoA desaturase. The specification does not present any examples wherein antisense targeted to human stearoyl-CoA desaturase was delivered to cells *in vivo* (whole organism), nor wherein antisense targeted to human stearoyl-CoA desaturase inhibited the expression of human stearoyl-CoA

desaturase in cells *in vivo* (whole organism). The specification does not provide any examples wherein treatment effects were obtained for any disease or condition, including a condition that involves abnormal lipid or cholesterol metabolism, atherosclerosis or cardiovascular disease using antisense targeted to human stearoyl-CoA desaturase.

The specification does not present any guidance on what specific diseases or conditions can be treated using antisense targeted to human stearoyl-CoA desaturase, including specific conditions that involve abnormal lipid or cholesterol metabolism, and specific types of cardiovascular disease, and what cells to target for a particular disease or condition. Although the art recognizes "there is substantial evidence linking SCD [stearoyl-CoA desaturase] activity to a wide range of disorders including obesity, diabetes, cardiovascular disease, skin disease, neurological disorders and cancer. However, the causal relationships between SCD [stearoyl-CoA desaturase] activity and these various disease states remain unclear." (Ntambi, J., J. Lipid Res. Vol 40, 1999, page 1551, second column, last paragraph, reference AG on PTO form 1449, filed June 4, 2002). Additionally, Ntambi et al. discuss the role of stearoyl-CoA in disease states wherein reduction of stearoyl-CoA is associated with the condition, for example, reduction of stearoyl-CoA activity can cause loss of myelination. The specification has not provided any antisense molecules to upregulate the expression of stearoyl-CoA, as may be required in many diseases and conditions.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder

the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed.

The specification provides examples wherein antisense is delivered to cells *in vitro* and the expression of human stearoyl-CoA desaturase is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to human stearoyl-CoA desaturase to generally any

target cell or tissue *in vivo* (whole organism) at a concentration effective to provide a pharmaceutical effect or to treat the broad range of diseases encompassed by the claims.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific diseases and conditions can be treated by the inhibition of the expression of human stearoyl-CoA desaturase, what specific cells to target with human stearoyl-CoA desaturase antisense for the treatment of a particular disease or condition, and how to specifically deliver antisense to a target cell *in vivo* (whole organism) at a concentration effective to result in inhibition of the expression of human stearoyl-CoA desaturase to a level sufficient to result in a pharmaceutical effect or to treat a disease. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo*. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods of treatment claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of treatment using antisense, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods of treatment and the lack of working

examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods of claims 15-20 over the full scope claimed without undue trial and error experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Stenn et al. (WO 00/09754, cited on PTO form 1449, filed June 4, 2002).

Stenn et al. discloses a 22-mer oligonucleotide that is fully complementary to SEQ ID NO:3 (see for example page 46). Stenn et al. disclose their oligonucleotide as a primer, however, based on the breadth of language "specifically hybridize" in the claim, the oligonucleotide primer disclosed by Stenn et al. meets all of the structural limitations of the claimed antisense compounds, since the sequence of the prior art oligo matches with 100% identity, and is within the recited size requirement for the

claimed oligo. Accordingly, the oligonucleotide primer disclosed by Stenn et al. would specifically hybridize as claimed. The burden of establishing whether the prior art oligos has the further function of inhibiting gene expression as claimed falls to applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596 (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above.

Therefore, Stenn et al. anticipates claims 1, 2, 11, 12 and 14.

Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Prouty et al. (US Pub. No. 2002/0151018).

Prouty et al. disclose a 22-mer and a 21-mer oligonucleotide (see for example, page 5, first column, first paragraph and page 5, second column, first paragraph) that are fully complementary to SEQ ID NO:3. Prouty et al. disclose these oligonucleotides

as primers, however, based on the breadth of language "specifically hybridize" in the claim, the oligonucleotide primers disclosed by Prouty et al. meet all of the structural limitations of the claimed antisense compounds, since the sequence of the prior art oligo matches with 100% identity, and is within the recited size requirement for the claimed oligo. Accordingly, the oligonucleotide primer disclosed by Prouty et al. would specifically hybridize as claimed. The burden of establishing whether the prior art oligos has the further function of inhibiting gene expression as claimed falls to applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596 (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above.

Therefore, Prouty et al. anticipates claims 1, 2, 11, 12 and 14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2 and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stenn et al. (WO 00/09754, cited on PTO form 1449, filed June 4, 2002) in view of Milner et al. and Baracchini et al. (US Patent No. 5,801,154).

Claims 1, 2 and 4-15 are drawn to an antisense compound 8-50 nucleotides in length targeted to a nucleic acid encoding human stearoyl-CoA desaturase, wherein the antisense comprises modified bases, including 5-methylcytosine modifications, modified sugars, including 2'-O-methoxyethyl modifications, internucleoside linkage modifications, including phosphorothioate, chimeric antisense, and compositions comprising said antisense and a pharmaceutically acceptable carrier, including a

colloidal dispersion system. The claims are further drawn to methods to inhibit the expression of human stearoyl-CoA desaturase in cells *in vitro*.

Stenn et al. teaches inhibiting the expression of human stearoyl-CoA desaturase using antisense expressed from a vector and teaches the full length sequence of a nucleic acid encoding human stearoyl-CoA desaturase, wherein the nucleic acid comprises SEQ ID NO:3 of the instant application (see, for example, figures 8 and 9 of Stenn et al.). Stenn et al. do not teach antisense targeted to a nucleic acid encoding human stearoyl-CoA desaturase of a length 8-50 nucleobases long. Stenn et al. do not teach antisense targeted to a nucleic acid encoding human stearoyl-CoA desaturase wherein the antisense comprises a modified backbone, a modified sugar, a 5-methylcytosine modified base or chimeric antisense molecules.

Baracchini et al. teach backbone modifications for antisense, including phosphorothioate modifications, 2'-O-methoxyethyl sugar modifications, 5-methyl cytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity and antisense oligonucleotides of 8-30 nucleotides in length. Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

Milner et al. teach methods of screening for determining antisense targeted to any known gene.

It would have been obvious to one of ordinary skill in the art to modify the vector expressed an antisense oligonucleotides targeted to a nucleic acid encoding human

stearoyl-CoA desaturase, as taught by Stenn et al., by making antisense a length within the range of 8-50 nucleobases (as taught by Baracchini et al.), because antisense of a short length are more easily synthesized and easier to deliver to cells and antisense of this length is conventional in the art. It would have been further obvious to make said antisense comprising modifications, including 2'-O-methoxyethyl, 5-methyl cytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, as taught by Baracchini et al., because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule (see for example Baracchini et al. column 6, paragraph 3). It would have been obvious to one of ordinary skill in the art to make a composition comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al., and because teach antisense expressed from a vector targeted to human stearoyl-CoA desaturase in compositions comprising a pharmaceutically acceptable carrier (see for example Stenn et al. page 16) for use, for example, in topically administered antisense.

One skilled in the art would have been motivated to make an antisense molecule targeted to a nucleic acid encoding human stearoyl-CoA desaturase because Stenn et al. teach inhibiting human stearoyl-CoA desaturase using antisense and one of ordinary skill in the art would be motivated to make such antisense of a length within the range of

8-50 nucleobases for ease of synthesis and delivery and because it is conventional in the art to make antisense within this range (as exemplified by Baracchini et al.). One of ordinary skill in the art would have been motivated to incorporate the modifications taught by Baracchini et al. for the benefits of stability and improved hybridization.

One skilled in the art would have expected to be able to find antisense which inhibits the expression of human stearoyl-CoA desaturase because the sequence of nucleic acids encoding human stearoyl-CoA desaturase, including SEQ ID NO:3 of the instant application, were known in the art and methods of screening for antisense to a known gene was routine (see for example Milner).

It would have been obvious to one of ordinary skill in the art to use antisense targeted to a nucleic acid encoding human stearoyl-CoA desaturase in a method of inhibiting the expression of human stearoyl-CoA desaturase in cells *in vitro* (cell culture), because it would be an obvious use for an antisense molecule designed to hybridize to and inhibit the expression of a nucleic acid encoding human stearoyl-CoA desaturase.

Therefore, the invention of claims 1, 2 and 4-15 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
January 11, 2003

KAREN LACOURCIERE
PATENT EXAMINER